REMARKS

Claims 1-54 are pending in the instant application. Claims 1-54 have been rejected. Claims 1-10, 14-15, 17-24, 27-28, 30-32, 37 and 44 have been amended. Claims 13 and 46-54 have been canceled. Claims 55-57 has been added. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Objections to the Specification

The Examiner suggests that the abstract of the Disclosure does not meet the requirements of the MPEP for US applications. Accordingly, Applicants have amended the abstract of the Disclosure to indicate the general nature of the claimed compounds as hydrophilic choline/N-heterocycle ester compounds. Support for this amendment is found at page 4 (lines 21-25), which describes the nature of the claimed compounds. It is therefore respectfully requested that this objection be reconsidered and withdrawn.

The Disclosure has been further objected to for failing to include a complete "Cross-References to Related Applications". Accordingly, Applicants have amended the first paragraph of the specification to include reference to the parent PCT application. It is therefore respectfully requested that this objection be reconsidered and withdrawn.

III. Objections to the Drawings

The drawings have been objected to by the Examiner as it is suggested that the drawings and particularly the pictures are frequently very small and difficult to understand because of the

consequent poor resolution. A larger format is suggested. It is further suggested that Figures 1 and 2 on their face and in their brief description fail to define the experimental conditions for the synthetic process steps labeled with bold face lower case letters. In an earnest effort to facilitate the prosecution of this application, Applicants submit herewith replacement drawings which illustrate the instant invention. Moreover, the brief description of Figures 1 and 2 have been amended as supported by Examples 1 and 2, respectively, to include the experimental conditions of the synthetic process steps. It is therefore respectfully requested that the objection to the drawings be reconsidered and withdrawn.

IV. Rejection of Claims Under 35 U.S.C. §112

Claims 1-54 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that Applicants rely on generic functional terminology including "amino acid derivative," "peptide comprising," and "having antioxidant activity" wherein the disclosure definition thereof does not overcome the functionality of the noted term or otherwise provide a basis for a complete definition of the metes and bounds of the claimed subject matter in the claim.

Applicants respectfully traverse this rejection.

"The 'written description' requirement ... serves both to satisfy the inventor's obligation to disclose the technologic

knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. ... The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).

Here, the Examiner argues that the specification does not adequately provide a basis for the complete definition of "amino acid derivative," "peptide comprising," and "having antioxidant activity" as used in the claimed invention, relying on the test defined by *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). That test, however, does not apply to every generic term recited in a claim. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003), "Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend."

Like the "vertebrate cells" and "mammalian cells" recited in the claims in *Amgen*, the terms "amino acid derivative," "peptide comprising," and "having antioxidant activity" recited in the instant claims are not new or unknown terms that ordinarily skilled artisans would easily miscomprehend. As in *Amgen*, the *Eli Lilly/Enzo Biochem* test that the Examiner relies on is inapposite here.

The specification generally describes amino acid and amino acid derivatives at lines 18-20 of page 8, and further provides

examples of amino acids (*e.g.*, glutamic acid, cysteine, and glycine) and amino acid derivatives (N-acetyl-cysteine and 2,2-dialkylthiazolidine) at lines 22-24 of page 8. Moreover, as evidenced by the teachings of Voet & Voet ((1990) In: *Biochemistry* pg. 71-73; copy attached for the Examiner's convenience), the phrase "amino acid derivative" is routinely used in the art to describe a modified amino acid residue. See page 71, column 1, paragraph under the heading "A. Amino Acid Derivatives in Proteins." As such, it would be readily apparent to one of skill in the art as to what constitutes an amino acid derivative.

Likewise, it is respectfully submitted that the phrase "peptide comprising" would be readily understood by one of skill in the art based upon the definition of "two or more amino acids or amino acid derivatives," which follows the phrase "peptide comprising." In addition, the paragraph spanning pages 8 and 9 clearly describes a peptide as "containing from two up to about ten amino acids or derivatives thereof, preferably from two up to about five amino acids or amino acid derivatives." Moreover, this passage provides specific examples of peptides within the scope of the invention, namely L-γ-glutamylcysteine, L-γ-glutamylglycine, L-cysteinylglycine, glutathione, L-carnosine, L-carnitine, and acetyl-L-carnitine, such that it would readily clear to one skilled in the art as to what constitutes a "peptide comprising."

With respect to amino acid, amino acid derivatives and peptides "having antioxidant activity," page 7 (lines 28-31) of the specification clearly describes the compounds of the invention as exerting an antioxidant effect, thereby reducing

reactive oxygen species. The specification and Figures further provide multiple examples of amino acids, amino acid derivatives and peptides having antioxidant activity. See, *e.g.*, paragraphs [0028]-[0029] and [0089]-[0096]. Given multiple examples and the specific effect of reducing reactive oxygen species, the skilled artisan would readily appreciate the metes and bounds of the claimed subject matter. It is therefore respectfully requested that this written description rejection of claims 1-54 be reconsidered and withdrawn.

Claims 1-54 have been further rejected under 35 U.S.C. § 112, first paragraph, for failing to meet the enablement requirement. It is suggested that, while the specification is enabled for making and testing for an anti-oxidant protective effect of a few choline esters of the compounds glutathione, N-acetyl cysteine, and cysteine, does not reasonably provide enablement for the large number of alternative structures, the biological testing thereof, and all the alternative syntheses claimed therefore. The Examiner alleges the breadth of the claims encompasses a very large number of compounds which have not been structurally identified, synthesized and/or tested for the capability to inhibit the adverse effects of oxidants on cell functions. It is suggested further that the prior art discloses compounds of the invention and that the ordinary practitioner would be expected to know how to make and how to test in a preliminary manner the compounds of the instant claims; however, in the absence of any disclosure for a test regimen involving a test host (*e.g.*, lower mammals), there is a low level of skill in determining whether the instant results are extrapolatable to the treatment of an actual disease condition as listed in claim 40 or

the effective inhibition of oxidative stress as in claims 38 and 45. It is acknowledged that the predictability of the synthetic portion of the claims is high in view of the well-known methods cited in the IDS; however, it is suggested that Example 11 is only prospective and therefore treatment of a disease has not been shown. The Examiner further alleges that because the disclosure only provides a few examples of compounds and some biological testing data, the quantity of experimentation needed to make or use the invention is deemed excessive. Applicants respectfully traverse this rejection.

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is not 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) (citation omitted, emphasis in original). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Applicants note that the Examiner acknowledges that the level of skill in the art is high (page 4, section D of the Office Action), the level of predictability in the synthetic portion is high (page 4, section E of the Office Action), and the disclosure provides examples of making and using the claimed compounds (page 4, section F of the Office Action). Yet, the Examiner maintains that one of skill could not practice the claimed invention. Specifically, it would appear that the premise of the Examiner's rejection is that the claims are excessively

broad and Applicants have not provided a working example of treatment. However, this should not be sufficient to invalidate a claim because "[a] claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such person to make and use the invention without undue experimentation." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 76 USPQ2d 1724, 1731 (Fed. Cir. 2005). Indeed, a claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. §112, first paragraph. *See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984), *In re Angstadt*, 537 F.2d 498, 502-3, (CCPA 1976), *In re Cook*, 439 F.2d 730, 732 (CCPA 1971).

Applicants have appreciated that by exploiting the characteristics of mitochondrial transport systems, such as choline transporters and the electrochemical potential gradient, hydrophilic choline/N-hetercoycle esters of glutathione and other peptide-and amino acid-based antioxidants can be concentrated in the mitochondria thereby providing critical mitochondrial antioxidant potential to counteract the effect of reactive oxygen species. See page 4, lines 21-25. While Applicants have not exemplified every possible compound within the scope of the

claims, a representative sample of the claimed compounds, their synthesis, and their use are provided. For example, paragraphs [0026]-[0035] provide general formulas which illustrate compounds of the present invention and paragraph [0036] provides more than a dozen specific examples of the claimed compounds. Furthermore, paragraphs [0040]-[0046] and Examples 1-2 provide examples of methods for synthesizing the claimed compounds and Examples 3-11 provide ample disclosure demonstrating efficacy of the claimed compounds for inhibiting oxidative stress-induced cell injury or death and treating conditions associated with oxidative stress-induced cell injury or death. Indeed, contrary to the Examiner's suggestion that Applicants have not demonstrated "treatment of actual disease conditions of the kind listed in claim 40" (page 4 section D of the Office Action), Example 7 specifically shows that mitochondrial targeted N-acetyl-L-cysteine improves post-ischemic recovery in rat heart subjected to ischemia-reperfusion, a disease condition specifically listed at line 4 of claim 40.

Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions. Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of patent bargain. *Invitrogen Corp. vs. Clontech Laboratories Inc.*, 77 USPQ2d at 1161-1174 (Fed. Cir. 2005).

Insofar as the breadth of the claims is concerned, it is well known that a "party asserting lack of compliance with the provisions of 35 U.S.C. [§] 112 has the burden of presenting cogent technical reasoning or objective evidence in support of

its position [,and such burden is not satisfied by] [m]erely pointing out that [the] claim is broad, in that it reads on undisclosed as well as disclosed embodiments. The mere fact that a claim embraces undisclosed or inoperative species or embodiments does not necessarily render it unduly broad." Horton v. Stevens, BPAI decision on March 08, 1988, *citing In re* Dinh-Nguven, 492 F.2d 856 (CCPA 1974); *In* re Bowen, 492 F.2d 859 (CCPA 1974); *In* re Smythe, 480 F.2d 1376 (CCPA 1973); *In* re Kamal, 398 F.2d 867 (CCPA 1968); and *In re* Sarett, 327 F.2d 1005 (CCPA 1964). In this regard, while the Examiner has implied that the claims embrace a vast array of compounds, the Examiner has not proffered a single compound, which is within the scope of the claims and goes beyond Applicants' disclosure.

With respect to the amount of experimentation, specific examples of the claimed compounds are given, and as noted above, the synthesis of such compounds are disclosed in the specification and, as acknowledged by the Examiner, would be well-known to one of ordinary skill in the art (page 4, section D. of the Office Action). Therefore, any experimentation would be minimal and routine. The Examiner has provided no evidence or reasoning, other than the very small number of examples provide by the disclosure, of why it would require an undue amount of experimentation by the skilled artisan to carry out the claimed invention given the guidance and working examples provided by the Specification.

Because as the specification provides ample and direct guidance for making and using the claimed invention, and furthermore provides a working example of treatment and inhibiting oxidative stress-induced cell injury or death,

enablement of the present invention under 35 U.S.C. § 112, first paragraph has been met. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

The disclosure has been objected to because the term "recover" is misspelled at page 6, line 17. Applicants have amended the specification at page 6 to correct this inadvertent typographical error. It is therefore respectfully requested that this objection be withdrawn.

Claims 1-10, 13-15, 17-24, 27-28, 30-32, 37-40, 44 and 46-54 have also been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particular point out and distinctly claim the subject matter which Applicants regard as the invention. It is suggested that the terms "amino acid" and "amino acid derivative having antioxidant activity" are technically erroneous (R is a substituent, not a separate compound required by the noted terms, and the noted terms fail to provide any definition of where in the structure of "R" substituent a bonding attachment occurs to the remainder of the generic formulas (I) and (II), thereby rending the claim incompletely defined. Applicants are directed to claims 1-10, 13-15, 17-24, and 27-38 wherein the above noted terms plus the terms "linker molecule," "hydrocarbon(s)," "N-heterocycle," "aromatic" and terms including same as their grammatical object. It is acknowledged that this rejection does not apply when the above terms are preceded by the term "group."

Applicants respectfully disagree with this rejection. However, in the interest of facilitating the prosecution of this application, the claims have been amended to indicate that the recited substituents are groups. Support for this amendment is

found in paragraph [0026]-[0035] and Figure 1 and 2 of the specification, which describe the various substituents of the present invention, as well as how said substituents are incorporated into the claimed compositions.

Claim 1 is further considered indefinite for containing a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation. Specifically, it is suggested that claim recites the broad recitation of "comprising" at line 6 and also recites "compound according to formula (I) or (II)" in line 1 and "containing" at line 8 which are narrower statements of the ranges/limitations applicable to the substituent definitions. Applicants respectfully disagree with this rejection. However, in an earnest effort to clarify, Applicants have amended claim 1 to recite "A compound comprising formula (I) or (II)", wherein R is "a peptide group, wherein said peptide group is two or more amino acids or amino acid derivatives, and has antioxidant activity."

Claim 13 is further considered indefinite for reciting the term "comprising" and being improperly dependent from claim 1. The Examiner suggests that the definition of "Z" in claim 1 needs to be expanded in some manner to include the subject matter of claim 13 and the noted term replaced by narrow language in claim 13. Applicants respectfully disagree. However, in the interest of facilitating the prosecution of this application, Applicants have amended claim 1 to include the subject matter of claim 13, and canceled claim 13.

Claims 30-31 have been suggested to be indefinite for recitation of the phrase "the N-heterocyclic amine comprising a quaternary nitrogen selected from the group consisting of

pyridinyl,… and pirazinyl" because the phrase is technically erroneous ("pirazinyl" is a misspelling of "pyridazinyl" or "pyrazinyl") and incomplete because the particular structures of the substituents being claimed are not completely described in either claim, *i.e.*, it is unclear what nitrogen is quaternary or whether multiple quaternary nitrogens are present. It is further noted that the term "comprising" renders the claims indefinite for failing to further limit the claim from which they depend. Applicants respectfully disagree with this rejection. However, in an earnest effort to clarify the structure of the claimed compounds, Applicants have amended claims 30 and 31 to be consistent with the disclosure at paragraph [0035] and claim 1, which indicates that when Q^2 is not present, the N-heterocycle possessing a quaternary nitrogen can be a pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, imidazolyl, or pyrazolyl. This passage further indicates that when Q^2 is present, the N-heterocycle possessing a quaternary nitrogen can be pyrrolyl, pyrrolidinyl, morpholinyl, or piperidinyl.

Claim 32 has been suggested to be indefinite for reciting the term "the compound according to claim 1." Accordingly, Applicants have amended claim 32 to clarify the nature of the pharmaceutical composition as containing "a compound according to claim 1."

Claims 37 and 44 have been rejected for reciting the phrase "compound is in the form of a pharmaceutical composition" because it is suggested that the phrase is misleading. Applicants respectfully disagree with this rejection. However, in the interest of clarifying how the compound is administered, Applicants have amended claims 37 and 44 to indicate that the

compound is in admixture with a pharmaceutically acceptable carrier as supported by claim 32 and the disclosure at pages 14-16.

Claim 40 has been suggested to indefinite for reciting the terms "neurodegenerative disease," "muscular disorders," "congenital mitochondrial disease," "neuromuscular degenerative disorders," and "aging-related diseases or disorder" because these terms lack sufficient further definition thereby rendering the claim incompletely defined. Applicants respectfully traverse this rejection.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, if "the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1987).

As clearly set forth at paragraph [0064] of the present specification, "neurodegenerative disease" is defined as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease and spinocerebellar ataxias; "muscular disorders" is defined as mitochondrial myopathy and lactic acidosis; "congenital mitochondrial disease" is defined as MELAS, LHON, Kearns-Sayres Syndrome, MERRF, NARP, and Leigh's Syndrome; "neuromuscular degenerative disorders" is defined as Friedreich's Ataxia, Duchenne muscular dystrophy, Multiple Sclerosis), epilepsy, neuropathy, neurological and neuropsychological developmental

delays, and amyotrophic lateral sclerosis; and "aging-related diseases or disorder" is defined as cognitive and motor disorders, progeria, and cancer. Accordingly, one skilled in the art would understand the bounds of the claim when read in light of the cited passage of the specification.

Claim 46 has been considered indefinite for recited the phrase "agents that are effective to remove one or more protecting groups." It is suggested that this phrase is generic and functional and therefore fails to define either the nature of the chemical groups being removed or the identity/identities of the "agent(s)" being claimed. Claims 47 is further noted as reciting "one or more protecting groups" and "cation scavenger agent" which have the same problem. Applicants respectfully disagree. Furthermore, the Examiner suggests that, as written, the process claims are provided in reverse order with the term of art "further comprising" rendering the claims confusing. Claims 51 and 52 have been rejected for containing limitations which make the claims impossible to understand. Claim 51 has also been rejected for reciting the term "I-Q^1" as the only reagent specified, when the structure "VIIIa" clearly suggests two process steps. Claim 53 has also been rejected for citing the term "protected glutathione" because the particular protecting groups have not been identified. The phrase "R' is a protected glutathione" and "R is L-cysteine" have been rejected in claims 53 and 54 because both terms are technically erroneous.

Applicants respectfully disagree with these rejections. However, in the interest of facilitating the prosecution of this application, Applicants have canceled claims 46-54 and present new claims 55-57, which clearly recites the essential steps in

producing a compound of formula (I) and formula (II). Support for this amendment is found in claims 45-54 as previously presented, paragraphs [0040]-[0046], Examples 1-2, and Figure 1-2. In so far as the protecting groups are routinely employed in the art and exemplified in Figures 1 and 2, it is respectfully submitted that one skilled in the art would understand the metes and bound of "protecting groups" in accordance with the present invention.

In light of these amendments and accompanying remarks, it is respectfully requested that the rejections of the claims under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

V. Double Patenting

Claims 1-54 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 11/312,873. It is acknowledged that the conflicting claims are not identical; however it is suggested that they are not patentably distinct because defined amino acid-choline ester derivatives, the pharmaceutical compositions thereof, the method of treatment wherein said amino acid-choline ester derivatives are administered, and the method of making said amino acid-choline esters are directed to substantially overlapping subject matter. The Examiner indicates that this a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants respectfully disagree with this rejection and request that this rejection be held in abeyance until allowable subject matter has been identified in copending Application No. 11/312,873.

VI. Rejection of Claims Under 35 U.S.C. §102

Claims 1-45 have been rejected under 35 U.S.C. 102(b) as being anticipated by Murphy et al. (PTO-1449 ref. 1A). It is alleged that claim 1 at column 20 of Murphy et al. anticipates the present invention. Applicants respectfully traverse this rejection.

"It is well settled that a claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998).

While claim 1 of Murphy et al. broadly claims a mitochondrially-targeted antioxidant compound comprising a lipophilic cation covalently coupled to an antioxidant moiety, wherein the antioxidant moiety is capable of being transported through the mitochondrial membrane and accumulated within the mitochondria of intact cells, with the proviso that the compound is not thiobutyltriphenylphosphonium bromide, this reference does not expressly or inherently disclose the compounds specifically defined by formula (I) and formula (II) of the present invention. Specifically, Murphy et al. do not disclose antioxidant amino acids, amino acid derivatives, or peptides thereof, nor does this reference suggest mitochondrial targeting via choline/N-heterocycle ester groups. Indeed, while the compounds of Murphy

et al. have a lipophilic cation, the compounds of the present invention are characterized as hydrophilic choline/N-heterocycle ester compounds. See page 4, lines 21-25. Because the compounds of the present invention are distinct from those of Murphy et al., this reference cannot be held to anticipate the present invention under 35 U.S.C. 102(b). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

VII. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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